Published in final edited form as:

Mol Aspects Med. 2015 November ; 45: 37–46. doi:10.1016/j.mam.2015.05.003.

RNA Biomarkers to Facilitate the Identification of Aggressive Prostate Cancer

Kathryn L. Pellegrini^a, Martin G. Sanda^a, and Carlos S. Moreno^{b,*}

^aDepartment of Urology at Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA 30322, USA

^bDepartment of Pathology and Laboratory Medicine at Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA 30322, USA

Abstract

A large number of men are diagnosed with prostate cancer each year, but many will not experience morbidity or mortality as a result of their cancers. Therefore, biomarkers for prostate cancer are necessary to carefully select patients for initial diagnostic biopsy or to facilitate care decisions for men who have already been diagnosed with prostate cancer. RNA-based approaches to biomarker discovery allow the investigation of non-coding RNAs, gene fusion transcripts, splice variants, and multi-gene expression panels in tissue, urine, or blood as opportunities to improve care decisions. This review focuses on RNA biomarkers that are available as commercial assays, and therefore already available for potential clinical use, as well as providing an overview of newer RNA biomarkers that are in earlier stages of clinical development.

Keywords

Prostate cancer; Biomarker; RNA; Non-coding RNA; lncRNA; Gene signatures

1. Introduction

Prostate cancer is the most common non-cutaneous cancer diagnosed in men, with over 200,000 diagnosed cases and almost 28,000 deaths per year in the United States (American Cancer Society, 2015). Biomarkers for prostate cancer are generally used in decisions to perform a prostate biopsy, to select the most appropriate treatment, and to monitor patient responses to treatment. One of the biggest obstacles in prostate cancer diagnosis and treatment is identifying patients with clinically significant cancer requiring aggressive treatment versus patients who have indolent cancers that are unlikely to progress.

*Corresponding author Emory University, Whitehead Biomedical Research Building, 615 Michael Street, Room 105J, Atlanta, GA 30322, USA Phone: +1 404-712-2809; Fax: +1 404-727-8538; cmoreno@emory.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Serum levels of prostate specific antigen (PSA) have been widely used in screening for the early detection of prostate cancer, resulting in the identification and treatment of more prostate cancers. However, the recent Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, and the European Randomised Study of Screening for Prostate Cancer (ERSPC) found little to no reduction in prostate cancer-specific mortality with systematic PSA screening as compared to opportunistic screening (Andriole et al., 2012; Schroder et al., 2012). Despite concerns about higher than anticipated levels of PSA screening occurring in the control group (Miller, 2012), the US Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer in all age groups as any ostensible benefits were outweighed by the associated risks of biopsy and over-treatment of indolent disease (Chou et al., 2011; Moyer and U.S. Preventive Services Task Force, 2012; Smith et al., 2015). Even so, serum PSA is still frequently used. Another PSA-based test, the Prostate Health Index (PHI), which combines total PSA, free PSA, and the [-2]proPSA precursor into a single score, was recently approved by the FDA for the detection of prostate cancer in men with total serum PSA values between 4 and 10 ng/mL, and a digital rectal exam (DRE) with no abnormal findings (Catalona et al., 2011). There are over one million prostate biopsies performed annually in Medicare beneficiaries in the US (which consists of men over the age of 65), and the number of biopsy cores retrieved during each procedure has increased from 6 to 12 (Loeb et al., 2011). However, prostate cancer is only found in one third of patients from initial biopsies, although cancer is eventually detected in two thirds of patients after up to four rounds of biopsy (Welch et al., 2007). These data indicate that there is potential to more accurately identify patients at risk of cancer to reduce unnecessary biopsies.

A number of clinical parameters are considered in directing treatment decisions for localized prostate cancer, but patients are generally grouped as having a low, intermediate, or high risk of progression based on serum PSA, tumor staging and Gleason scoring of the biopsy sample (D'Amico et al., 2003). Results from the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) and the Prostate Cancer Intervention Versus Observation (PIVOT) trial indicate that observation may be a better approach than radical prostatectomy for patients with low risk prostate cancer, especially for patients over 65 years in age (Bill-Axelsson et al., 2014; Wilt et al., 2012). In contrast, men with high risk cancers, or a longer life expectancy are more likely to benefit from the immediate initiation of curative intent therapies such as radical prostatectomy, external beam radiation therapy, or brachytherapy (Bill-Axelsson et al., 2014; Wilt et al., 2012). However, complications such as urinary incontinence or sexual dysfunction commonly impact health-related quality of life following these types of curative interventions for prostate cancer, and emphasize the importance of accurately discerning patients at risk of prostate cancer-specific mortality (Potosky et al., 2000; Sanda et al., 2008). While the identification of men with low risk cancers is generally accomplished very well using current clinical parameters, there are many men with intermediate risk cancers that will not experience progression of their tumors. If there were biomarkers available that were better able to distinguish amongst patients diagnosed with intermediate risk prostate cancers to identify men that have low or high probability of experiencing prostate cancer-associated morbidity and mortality, curative interventions could be more specifically directed to avoid over-treatment of indolent cancers.

The measurement of gene expression is an attractive source for the discovery of biomarkers because it allows the evaluation of tumor activity, potentially identifying various molecular subtypes of cancer. Although both protein and RNA provide information about molecular activity, RNA is generally much easier to detect and quantitate, even at low amounts. Additionally, the multiplexing of RNA-based assays is relatively straightforward, which means that many targets can be assessed at once. RNA-based approaches to prostate cancer biomarker discovery include the analysis of non-coding RNAs, gene fusion transcripts, alterations in the presence of splice variants, and multi-gene expression panels based on various tumor cell functions. For many of these targets, expression in urine, blood, or circulating tumor cells have also been investigated as a way to non-invasively detect or track prostate cancer.

2. Non-Coding RNAs

Although the majority of the genome is transcribed, only a fraction of these transcripts are protein-coding and, the ongoing annotation of non-coding RNAs (ncRNAs) means that the non-coding subset of RNA represents a growing resource for the identification of disease-associated genes (Iyer et al., 2015; The ENCODE Project Consortium, 2007). GENCODE v21 contains annotations for 9,534 small non-coding RNAs, which are less than 200 nucleotides in length and include a number of distinct categories such as microRNAs (miRNAs) and small nucleolar RNAs (snoRNAs), while the long non-coding RNA (lncRNA) compartment, defined as being longer than 200 nucleotides, is composed of 15,877 lncRNA genes encoding for 26,414 lncRNA transcripts (Derrien et al., 2012; Harrow et al., 2012). However, recent reports suggest that there may be closer to 60,000 lncRNA genes in the human genome (Iyer et al., 2015). The study of ncRNA biomarkers in prostate cancer has been predominantly focused on the lncRNA PCA3, although the continued discovery and annotation of ncRNAs in the human genome means it is likely that many more ncRNAs will be found to have an association with prostate cancer.

2.1. PCA3

The most well characterized of the next generation of prostate cancer biomarkers is the lncRNA PCA3, which recently received FDA approval for decisions about repeat biopsy (Groskopf et al., 2006). The over-expression of PCA3 in prostate cancer was originally established by differential display analysis of patient-matched malignant and benign tissues collected during radical prostatectomy, where it was found to be 10- to 100-fold higher in the cancerous tissues for 53 of the 56 patients studied (Bussemakers et al., 1999). Another aspect of PCA3 that made it an attractive biomarker candidate was the absence of PCA3 expression in normal or malignant tissues of non-prostate origin, including genitourinary sources such as kidney, bladder, seminal vesicles, and testis (Bussemakers et al., 1999; de Kok et al., 2002). Additionally, PCA3 expression was not increased in patients diagnosed with prostate conditions other than cancer such as benign prostatic hyperplasia (BPH), atypical small acinar proliferation (ASAP), prostatic intraepithelial neoplasia (PIN), inflammation, or chronic prostatitis (de Kok et al., 2002; Deras et al., 2008; Vlaeminck-Guillem et al., 2012). The feasibility of PCA3 as a urinary biomarker was first demonstrated by qRT-PCR analysis of urinary sediments from a cohort of 108 men that had been

recommended for prostate biopsy based on a serum PSA greater than 3 ng/mL (Hessels et al., 2003).

A clinical grade assay, currently available as the Progen[®] PCA3 Assay from Hologic Gen-Probe[™], has now been developed and used to investigate the urinary expression of PCA3 in a number of large cohorts. This assay utilizes transcription-mediated amplification to quantify PSA and PCA3 transcripts in whole urine collected post-DRE, so that a PCA3 score can be calculated (Groskopf et al., 2006). Patients with high urinary PCA3 scores have a greater likelihood of being diagnosed with prostate cancer on biopsy (Aubin et al., 2010; Crawford et al., 2012; Deras et al., 2008; Gittelman et al., 2013; Ramos et al., 2013; van Gils et al., 2007), and urinary PCA3 has shown similar diagnostic performance for patients in either high or low serum PSA ranges (Chevli et al., 2014; Deras et al., 2008; Groskopf et al., 2006; Haese et al., 2008; Stephan et al., 2013; Tinzi et al., 2004). Therefore, the added consideration of urinary PCA3 scores can significantly improve the performance of diagnostic models based on clinical variables such as age, family history, prostate volume, DRE findings, and PSA (Aubin et al., 2010; Gittelman et al., 2013; Hansen et al., 2013; Tombal et al., 2013; Wei et al., 2014). In one recent study, the performance of the PCPT (Prostate Cancer Trials and Prevention) risk calculator for the detection of any prostate cancer and high-grade prostate cancer was significantly improved by including the PCA3 score into the model (Wei et al., 2014). Other studies have found that incorporating PCA3 scores with the PSA-based PHI score shows a higher specificity for the detection of prostate cancer on biopsy than either marker alone or over base models that incorporate standard clinical variables (Ferro et al., 2013; Perdoni et al., 2013; Stephan et al., 2013). Although PCA3 has shown improved specificity for the detection of prostate cancer when compared to serum PSA, the lower sensitivity of PCA3 means that it is insufficient as a stand-alone biomarker for decisions regarding initial biopsy. However, as shown in a number of the studies discussed here, the inclusion of PCA3 can improve the performance of other clinical factors, which demonstrates the potential for additional biomarkers to provide complementary information during the diagnosis of prostate cancer.

2.2. Additional Non-Coding RNAs Under Investigation

A number of additional ncRNAs, including both miRNAs and lncRNAs, have been studied for their association with prostate cancer and potential use as biomarkers (summarized in Table 1). Although these ncRNAs are still in a much earlier stage of understanding and development than PCA3, they have all been investigated in multiple, independently collected cohorts, some of which include very large numbers of participants. However, their performance in these retrospective studies will need to be carefully considered before attempting to test their performance in prospective multicenter trials. Of these ncRNAs, the current evidence for SChLAP1 is most convincing, given that this lncRNA has shown prognostic performance across multiple prostate cancer outcomes including biochemical recurrence, metastasis, and mortality, and was also able to be detected in urine sediments (Prensner et al., 2014b).

3. Gene Rearrangements and Splice Variants

Chromosomal aberrations such as deletions and translocations are frequently observed in cancer, and can often lead to changes in the expression of oncogenes or tumor suppressors. One of the best characterized gene fusions, BCR-ABL, is the result of a chromosomal translocation (also known as the Philadelphia chromosome) commonly observed in chronic myeloid leukemia that is used as a biomarker during diagnosis, and as a biomarker for monitoring patient response during treatment (Rowley, 2001). In contrast, alternative splicing of genes is a normal molecular event that enables different versions of a gene to be expressed and translated. However, there are a number of splicing abnormalities that occur in cancer, including both transcriptome-wide changes in splicing events during cancer and the expression of particular splice variants in specific cancers (Kalnina et al., 2005; Sowalsky et al., 2015; Venables et al., 2009). Gene rearrangements and splice variants are not always able to be detected on microarray, but the use of RNA sequencing for gene expression profiling means that these types of changes can be more clearly recognized and studied for the identification of biomarkers.

3.1. TMPRSS2:ERG Fusion

The ETS transcription family members and proto-oncogenes, ERG and ETV1, were found to be highly expressed in a subset of prostate cancers by Tomlins et al. (2005) using a unique approach, which they termed cancer outlier profile analysis (COPA), to interrogate the Oncomine database. Genetic analysis of prostate cancer cell lines with over-expression of these genes found the 5' end of the androgen receptor-regulated gene TMPRSS2 to be aberrantly fused to either ERG or ETV1, which was confirmed by FISH in clinical samples for both TMPRSS2:ETV1 (7 out of 29 cases) and TMPRSS2:ERG (16 out of 29 cases) (Tomlins et al., 2005). Follow up studies have shown TMPRSS2:ERG gene rearrangements to be the most commonly found TMPRSS2:ETS family pairing in prostate cancer, although the frequency of this fusion varies significantly amongst different racial groups (Magi-Galluzzi et al., 2011; Tomlins et al., 2006). In Caucasian cohorts, TMPRSS2:ERG fusion is observed in approximately 50% of prostate cancers, whereas in African American or Asian cohorts, the frequency of TMPRSS2:ERG ranges from 20-30% (Khani et al., 2014; Magi-Galluzzi et al., 2011; Miyagi et al., 2010; Mosquera et al., 2009; Rosen et al., 2012). TMPRSS2:ERG fusions are rarely observed in benign tissue, but are observed in areas of high grade prostatic epithelial neoplasia (HGPIN) in close proximity to a concurrent cancer of the same TMPRSS2:ERG status (Cerveira et al., 2006; Mosquera et al., 2008; Perner et al., 2007; Young et al., 2012). Additionally, ERG expression in HGPIN lesions was found to be indicative of subsequent prostate cancer diagnosis with patients positive for ERG expression in their HGPIN lesions significantly more likely to be diagnosed with prostate cancer within three years (Park et al., 2014). These studies demonstrate the specificity of TMPRSS2:ERG for prostate cancer and indicate a role for TMPRSS2:ERG in the development and progression of prostate cancer, which could be applied as a biomarker to identify patients with HGPIN lesions that have a higher likelihood of progressing to prostate cancer.

The association of the TMPRSS2:ERG fusion with more aggressive tumor characteristics is currently unclear, with some studies claiming significant relationships of TMPRSS2:ERG status with Gleason score, biochemical recurrence, and survival (Attard et al., 2008; Demichelis et al., 2007; Lin et al., 2013; Nam et al., 2007), and others finding no significant differences related to the gene fusion (Hoogland et al., 2012; Minner et al., 2011; Perner et al., 2006; Pettersson et al., 2012). However, the combination of urinary TMPRSS2:ERG with PCA3, serum PSA, or with other clinical risk determinants has been shown to improve the identification of high-grade cancer (Attard et al., 2008; Leyten et al., 2014; Tomlins et al., 2011). In a multicenter cohort of 1,065 men receiving prostate biopsies at community and academic medical centers, patients in the group with the highest combined TMPRSS2:ERG and PCA3 scores had a 3.2-fold higher chance of being diagnosed with cancer, and a 5.9-fold greater chance of having high-grade cancer (Gleason score greater than 6) when compared to the group with the lowest scores (Tomlins et al., 2011). A separate multicenter study of 443 men found that using both PCA3 and TMPRSS2:ERG (with score thresholds of 25 and 10, respectively), would have avoided 153 biopsies (35%) in men that would have otherwise been recommended for prostate biopsy based on their serum PSA levels alone, while missing only 11 (10%) of the high-grade prostate cancers (Leyten et al., 2014). Additionally, including both the TMPRSS2:ERG and PCA3 scores with the PCPT or ERSPC risk calculators significantly improved the performance of these clinical parameters for the detection of patients at higher risk of having prostate cancer prior on biopsy (Leyten et al., 2014; Tomlins et al., 2011). Now that a urine test for TMPRSS2:ERG is commercially available using the same assay platform as PCA3, the advantages of combining these biomarkers for the detection of prostate cancer can be investigated further.

3.2. AR-V7 Splice Variants

Given the importance of the androgen receptor (AR) in the development, progression, and treatment of prostate cancer, the molecular aspects of the AR have been studied extensively with up to 14 different AR splice variants identified thus far (Dehm et al., 2008; Guo et al., 2009; Hu et al., 2009; Hu et al., 2011; Sun et al., 2010; Watson et al., 2010). The majority of studies have focused on the AR-V7 splice variant (also previously referred to as AR3), which has been confirmed to produce a functional protein that is constitutively localized to the nucleus and therefore able to induce the expression of AR-regulated genes such as PSA and TMPRSS2 in the absence of androgens (Guo et al., 2009; Hu et al., 2009; Hu et al., 2011; Watson et al., 2010). This is important in the context of androgen deprivation therapy (ADT), particularly as it has been shown in human cell lines and xenograft tumor models that AR-V7 expression increases in response to castration or other treatments targeting the AR, and that AR-V7 over-expression promotes androgen-independent growth (Guo et al., 2009; Hu et al., 2012; Li et al., 2012; Watson et al., 2010). In clinical specimens, high levels of AR-V7 expression are more frequently observed in patients that have previously received ADT, but then progressed to metastatic castration resistant prostate cancer (mCRPC) (Antonarakis et al., 2014; Hornberg et al., 2011; Hu et al., 2009; Qu et al., 2015; Zhang et al., 2011). The expression of AR-V7 in primary tumors or metastases has been correlated with significantly worse clinical outcomes, including reduced time to biochemical recurrence (Guo et al., 2009; Hu et al., 2009), and earlier cancer-specific mortality

(Antonarakis et al., 2014; Hornberg et al., 2011; Qu et al., 2015). More recently, AR-V7 expression in circulating tumor cells (CTCs) was shown to be predictive of patient responses to the AR-targeted treatments enzalutamide or abiraterone for the treatment of mCRPC (Antonarakis et al., 2014). Strikingly, none of the patients positive for AR-V7 expression in their CTCs showed a response to either enzalutamide or abiraterone treatment as measured by percentage change in PSA level, while amongst patients with AR-V7 negative CTCs, the response rate was 53% (10 out of 19 patients) for enzalutamide and 68% (17 out of 25 patients) for abiraterone (Antonarakis et al., 2014). Regardless of treatment group, patients positive for AR-V7 also experienced a significantly reduced progression-free survival time as measured by PSA, clinical or radiographic measures, as well as a significantly reduced overall survival (Antonarakis et al., 2014). Although these findings need to be investigated in a larger cohort, they suggest that the expression of AR-V7 in CTCs could be used as a predictive biomarker to inform treatment decisions in mCRPC, particularly in identifying patients that are unlikely to respond to enzalutamide or abiraterone, and therefore need to consider more appropriate treatment strategies.

4. Multi-Gene mRNA Expression Panels

As high-throughput gene analysis has become more accessible, the development and analysis of multi-gene panels in clinical samples has become more feasible. This is especially important in conditions such as cancer, where there is a high degree of heterogeneity both at the molecular level within the tumor, as well as between individual patients (Fraser et al., 2015; Singh et al., 2002). One way to overcome this heterogeneity is to profile the expression of multiple genes at once to establish the molecular processes occurring in the tumor. Although many multi-gene expression panels have been described, we have mostly focused on those that are commercially available for the analysis of biopsy or prostatectomy tissue as LDTs (Laboratory-Developed Tests) under CLIA (Clinical Laboratory Improvement Amendments) certification. While the three commercially available panels described here (and summarized in Table 2) have all been thoroughly assessed for their prognostic ability in stratifying patients at risk of biochemical recurrence or metastasis after primary treatment, ideally further testing would test their predictive value in decisions about treatment to more clearly link these risk scores with particular therapeutic outcomes, which would allow these tests to be used in a predictive capacity during treatment decisions.

4.1. Cell Cycle Progression Score

The prognostic potential of proliferation markers such as cyclins and Ki67 in prostate cancer has been established in studies utilizing immunoreactivity to determine the expression of these markers in prostatectomy tissues and lymph node metastases (Bubendorf et al., 1996; Cheng et al., 1999; Khor et al., 2009; Mashal et al., 1996). More recently, Cuzick et al. (2011) used a candidate gene approach to select and test a panel of 126 cell cycle and cellular proliferation genes in RNA extracted from FFPE prostate tumor tissues. A refined panel of 31 highly correlated genes was developed to robustly measure proliferation within the tumor, with the information provided from the analysis of these 31 genes termed the cell cycle progression (CCP) score (Cuzick et al., 2011). A retrospective determination of CCP

scores from 366 radical prostatectomy cases and 337 transurethral resection of the prostate cases found that patients with higher CCP scores had a higher probability of biochemical recurrence or death over a 10-year follow-up period (Cuzick et al., 2011). This test, currently commercially available as Prolaris® from Myriad Genetics, also has demonstrated efficacy in prostate tissue obtained from biopsy (Bishoff et al., 2014; Cuzick et al., 2012; Freedland et al., 2013). From these studies, high CCP scores from biopsy were significantly associated with reduced time to biochemical recurrence, development of metastases, or death from prostate cancer (Bishoff et al., 2014; Cuzick et al., 2012). Additionally, the CCP score provided information independent from other clinical variables such as PSA or Gleason score, which meant that patients could be further stratified when the CCP score was combined with these clinical parameters to create an overall risk score for the identification of patients at risk of biochemical recurrence (Cooperberg et al., 2013; Cuzick et al., 2012; Freedland et al., 2013).

4.2. Genomic Prostate Score

In another study utilizing a candidate gene approach, Klein et al. (2014) analyzed the expression of 727 genes in two separate tumor specimens from 441 radical prostatectomy patients, allowing the predictive ability of these genes to be compared in tissues corresponding to either the primary or highest Gleason score. Of the 228 genes found to be associated with biochemical recurrence regardless of Gleason pattern, 81 genes were selected for further evaluation in a separate biopsy cohort to create a final gene signature, which includes genes representative of stromal response, cellular organization, proliferation, and androgen signaling (Klein et al., 2014). Gene expression levels of the 12 genes included in this signature are used to calculate the genomic prostate score (GPS), which has now been analytically validated and is commercially available as the Oncotype DX® Prostate Cancer Assay from Genomic Health (Knezevic et al., 2013). Although GPS distribution was significantly increased in patients scoring higher by other clinical risk determinants such as CAPRA (Cancer of the Prostate Risk Assessment) or NCCN (National Comprehensive Cancer Network) criteria, the GPS values within each clinical risk strata overlapped to a great extent (Cullen et al., 2014; Klein et al., 2014). This meant that the GPS provided additional benefit to traditional risk assessment as demonstrated by the continued significant association of the GPS with the increased likelihood of discovering adverse pathology on prostatectomy, or of biochemical recurrence following prostatectomy, even after adjusting for the inclusion of these clinical risk parameters (Cullen et al., 2014; Klein et al., 2014).

4.3. Genomic Classifier

With the objective of identifying a gene signature that would be predictive of rapid metastasis, Erho et al. (2013) conducted microarray analysis to determine gene expression in the prostate tumor tissues of patients that had developed metastases within five years of biochemical recurrence as compared to a control group of patients that either had no evidence of metastases after biochemical recurrence or had not experienced biochemical recurrence. The final gene signature consisting of 22 genes is combined to create a single Genomic Classifier (GC) score in which higher scores indicate a higher likelihood of metastasis (Erho et al., 2013). This GC score is currently commercially available as the Decipher® Prostate Cancer Classifier from GenomeDx. Higher GC scores were significantly

associated with a greater likelihood of biochemical recurrence and metastasis, even after adjusting for other associated clinical variables such as Gleason score, seminal vesicle invasion, and extraprostatic extension (Den et al., 2014; Erho et al., 2013; Karnes et al., 2013; Klein et al., 2015; Ross et al., 2014). The rapid appearance of metastatic disease is significantly associated with a reduced time until prostate cancer-specific death, which demonstrates the importance of biomarkers such as the GC score that could be used to identify patients at higher risk of prostate cancer-specific mortality that may require more aggressive treatment following prostatectomy (Cooperberg et al., 2015; Klein et al., 2015).

4.4. Additional Gene Signatures of Indolence and Aggression

Aside from the commercially available gene panels, a number of other groups have established gene signatures prognostic for biochemical recurrence or mortality, using methods such as candidate gene approaches to investigate particular pathways (Irshad et al., 2013; Peng et al., 2014), and whole transcriptome analysis either by microarray (Gasi Tandefelt et al., 2013; Yu et al., 2004) or RNA sequencing (Long et al., 2014). A collection of the gene signatures that have been described are summarized in Table 3, and include panels that have demonstrated prognostic ability for either biochemical recurrence or mortality. Although there have been many studies investigating the gene expression profile of prostate cancers, the criteria for inclusion here was that a defined gene signature had to have been identified and validated in cohorts collected at multiple institutions. These expression panels include gene signatures that were developed with a focus on low-risk cancers, subsequently improving the identification of biochemical recurrence or mortality amongst patients with Gleason 7 cancers (Irshad et al., 2013; Penney et al., 2011), as well as a gene signature that outperformed the CCP score in identifying men at risk of biochemical recurrence (Long et al., 2014).

5. Conclusions

Amongst the RNA biomarkers described here are biomarkers with the potential to be used in all stages of prostate cancer management, from detection (PCA3, TMPRSS2:ERG), directing treatment (AR-V7), and prognosis (Prolaris[®], Oncotype DX[®], Decipher[®]). Additionally, there are a number of RNAs in earlier stages of investigation with potential application as biomarkers of recurrence, metastasis, and indolence. The continued analysis of these and other biomarkers is important to fully define parameters that could be used to determine the most appropriate course of treatment for each patient, with the understanding that prostate cancer is a very heterogeneous disease. It is likely that a number of factors, including current clinical parameters such as age, family history, and pathology, will need to be combined with additional molecular biomarkers to provide the best characterization of each patient's cancer and their risk of progression. It is also important to consider that, while patients can be wary of leaving their cancer "untreated," the best course of action may not necessarily be curative intent treatment. However, if these biomarkers can be clearly linked to particular treatment outcomes, as is the case for the AR-V7 splice variant, patients and physicians will be able to decide upon an appropriate course of action with greater confidence.

Acknowledgements

This work was supported by NCI Cancer Center Support Grant P30CA138292 and NIH U01CA113913.

6. References

- American Cancer Society. Cancer Facts & Figures 2015. Atlanta: 2015.
- Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, Fouad MN, Isaacs C, Kvale PA, Reding DJ, Weissfeld JL, Yokochi LA, O'Brien B, Ragard LR, Clapp JD, Rathmell JM, Riley TL, Hsing AW, Izmirlian G, Pinsky PF, Kramer BS, Miller AB, Gohagan JK, Prorok PC. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst.* 2012; 104(2):125–132. [PubMed: 22228146]
- Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, Chen Y, Mohammad TA, Chen Y, Fedor HL, Lotan TL, Zheng Q, De Marzo AM, Isaacs JT, Isaacs WB, Nadal R, Paller CJ, Denmeade SR, Carducci MA, Eisenberger MA, Luo J. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med.* 2014; 371(11):1028–1038. [PubMed: 25184630]
- Attard G, Clark J, Ambrosini L, Fisher G, Kovacs G, Flohr P, Berney D, Foster CS, Fletcher A, Gerald WL, Moller H, Reuter V, De Bono JS, Scardino P, Cuzick J, Cooper CS, Transatlantic Prostate G. Duplication of the fusion of TMPRSS2 to ERG sequences identifies fatal human prostate cancer. *Oncogene.* 2008; 27(3):253–263. [PubMed: 17637754]
- Aubin SM, Reid J, Sarno MJ, Blase A, Aussie J, Rittenhouse H, Rittmaster R, Andriole GL, Grosskopf J. PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial. *J Urol.* 2010; 184(5):1947–1952. [PubMed: 20850153]
- Bill-Axelsson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, Nordling S, Haggman M, Andersson SO, Spangberg A, Andren O, Palmgren J, Steineck G, Adami HO, Johansson JE. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med.* 2014; 370(10):932–942. [PubMed: 24597866]
- Bishoff JT, Freedland SJ, Gerber L, Tennstedt P, Reid J, Welbourn W, Graefen M, Sangale Z, Tikishvili E, Park J, Younus A, Gutin A, Lanchbury JS, Sauter G, Brawer M, Stone S, Schlomm T. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. *J Urol.* 2014; 192(2):409–414. [PubMed: 24508632]
- Bismar TA, Demichelis F, Riva A, Kim R, Varambally S, He L, Kutok J, Aster JC, Tang J, Kuefer R, Hofer MD, Febbo PG, Chinnaiyan AM, Rubin MA. Defining aggressive prostate cancer using a 12-gene model. *Neoplasia.* 2006; 8(1):59–68. [PubMed: 16533427]
- Brase JC, Johannes M, Schlomm T, Falth M, Haese A, Steuber T, Beissbarth T, Kuner R, Sultmann H. Circulating miRNAs are correlated with tumor progression in prostate cancer. *Int J Cancer.* 2011; 128(3):608–616. [PubMed: 20473869]
- Bubendorf L, Sauter G, Moch H, Schmid HP, Gasser TC, Jordan P, Mihatsch MJ. Ki67 labelling index: an independent predictor of progression in prostate cancer treated by radical prostatectomy. *J Pathol.* 1996; 178(4):437–441. [PubMed: 8691323]
- Bussemakers MJ, van Bokhoven A, Verhaegh GW, Smit FP, Karthaus HF, Schalken JA, Debruyne FM, Ru N, Isaacs WB. DD3: a new prostate-specific gene, highly overexpressed in prostate cancer. *Cancer Res.* 1999; 59(23):5975–5979. [PubMed: 10606244]
- Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, Slawin KM, Marks LS, Loeb S, Broyles DL, Shin SS, Cruz AB, Chan DW, Sokoll LJ, Roberts WL, van Schaik RH, Mizrahi IA. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. *J Urol.* 2011; 185(5):1650–1655. [PubMed: 21419439]
- Cerveira N, Ribeiro FR, Peixoto A, Costa V, Henrique R, Jeronimo C, Teixeira MR. TMPRSS2-ERG gene fusion causing ERG overexpression precedes chromosome copy number changes in prostate carcinomas and paired HGPIN lesions. *Neoplasia.* 2006; 8(10):826–832. [PubMed: 17032499]

- Chakravarty D, Sboner A, Nair SS, Giannopoulou E, Li R, Hennig S, Mosquera JM, Pauwels J, Park K, Kossai M, MacDonald TY, Fontugne J, Erho N, Vergara IA, Ghadessi M, Davicioni E, Jenkins RB, Palanisamy N, Chen Z, Nakagawa S, Hirose T, Bander NH, Beltran H, Fox AH, Elemento O, Rubin MA. The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer. *Nat Commun.* 2014; 5:5383. [PubMed: 25415230]
- Cheng HH, Mitchell PS, Kroh EM, Dowell AE, Chery L, Siddiqui J, Nelson PS, Vessella RL, Knudsen BS, Chinnaiyan AM, Pienta KJ, Morrissey C, Tewari M. Circulating microRNA profiling identifies a subset of metastatic prostate cancer patients with evidence of cancer-associated hypoxia. *PLoS ONE.* 2013; 8(7):e69239. [PubMed: 23935962]
- Cheng L, Pisansky TM, Sebo TJ, Leibovich BC, Ramnani DM, Weaver AL, Scherer BG, Blute ML, Zincke H, Bostwick DG. Cell proliferation in prostate cancer patients with lymph node metastasis: a marker for progression. *Clin Cancer Res.* 1999; 5(10):2820–2823. [PubMed: 10537347]
- Chevli KK, Duff M, Walter P, Yu C, Capuder B, Elshafei A, Malczewski S, Kattan MW, Jones JS. Urinary PCA3 as a predictor of prostate cancer in a cohort of 3,073 men undergoing initial prostate biopsy. *J Urol.* 2014; 191(6):1743–1748. [PubMed: 24333241]
- Chou R, Crosswell JM, Dana T, Bougatsos C, Blazina I, Fu R, Gleitsmann K, Koenig HC, Lam C, Maltz A, Ruge JB, Lin K. Screening for prostate cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2011; 155(11):762–771. [PubMed: 21984740]
- Cooperberg MR, Davicioni E, Crisan A, Jenkins RB, Ghadessi M, Karnes RJ. Combined Value of Validated Clinical and Genomic Risk Stratification Tools for Predicting Prostate Cancer Mortality in a High-risk Prostatectomy Cohort. *Eur Urol.* 2015; 67(1):326–333. [PubMed: 24998118]
- Cooperberg MR, Simko JP, Cowan JE, Reid JE, Djalilvand A, Bhatnagar S, Gutin A, Lanchbury JS, Swanson GP, Stone S, Carroll PR. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J Clin Oncol.* 2013; 31(11):1428–1434. [PubMed: 23460710]
- Crawford ED, Rove KO, Trabulsi EJ, Qian J, Drewnowska KP, Kaminetsky JC, Huisman TK, Bilowus ML, Freedman SJ, Glover WL Jr, Bostwick DG. Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases. *J Urol.* 2012; 188(5):1726–1731. [PubMed: 22998901]
- Cullen J, Rosner IL, Brand TC, Zhang N, Tsiatis AC, Moncur J, Ali A, Chen Y, Knezevic D, Maddala T, Lawrence HJ, Febbo PG, Srivastava S, Sesterhenn IA, McLeod DG. A Biopsy-based 17-gene Genomic Prostate Score Predicts Recurrence After Radical Prostatectomy and Adverse Surgical Pathology in a Racially Diverse Population of Men with Clinically Low- and Intermediate-risk Prostate Cancer. *Eur Urol.* 2014 10.1016/j.eururo.2014.11.030.
- Cuzick J, Berney DM, Fisher G, Mesher D, Moller H, Reid JE, Perry M, Park J, Younus A, Gutin A, Foster CS, Scardino P, Lanchbury JS, Stone S, Transatlantic Prostate G. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer.* 2012; 106(6):1095–1099. [PubMed: 22361632]
- Cuzick J, Swanson GP, Fisher G, Brothman AR, Berney DM, Reid JE, Mesher D, Speights VO, Stankiewicz E, Foster CS, Moller H, Scardino P, Warren JD, Park J, Younus A, Flake DD 2nd, Wagner S, Gutin A, Lanchbury JS, Stone S. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol.* 2011; 12(3):245–255. [PubMed: 21310658]
- D'Amico AV, Cote K, Loffredo M, Renshaw AA, Chen MH. Pretreatment predictors of time to cancer specific death after prostate specific antigen failure. *J Urol.* 2003; 169(4):1320–1324. [PubMed: 12629352]
- de Kok JB, Verhaegh GW, Roelofs RW, Hessels D, Kiemeny LA, Aalders TW, Swinkels DW, Schalken JA. DD3(PCA3), a very sensitive and specific marker to detect prostate tumors. *Cancer Res.* 2002; 62(9):2695–2698. [PubMed: 11980670]
- Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. *Cancer Res.* 2008; 68(13):5469–5477. [PubMed: 18593950]
- Demichelis F, Fall K, Perner S, Andren O, Schmidt F, Setlur SR, Hoshida Y, Mosquera JM, Pawitan Y, Lee C, Adami HO, Mucci LA, Kantoff PW, Andersson SO, Chinnaiyan AM, Johansson JE,

- Rubin MA. TMPRSS2:ERG gene fusion associated with lethal prostate cancer in a watchful waiting cohort. *Oncogene*. 2007; 26(31):4596–4599. [PubMed: 17237811]
- Den RB, Feng FY, Showalter TN, Mishra MV, Trabulsi EJ, Lallas CD, Gomella LG, Kelly WK, Birbe RC, McCue PA, Ghadessi M, Yousefi K, Davicioni E, Knudsen KE, Dicker AP. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. *Int J Radiat Oncol Biol Phys*. 2014; 89(5):1038–1046. [PubMed: 25035207]
- Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, Ellis WJ, Marks LS, Fradet Y, Rittenhouse H, Groskopf J. PCA3: a molecular urine assay for predicting prostate biopsy outcome. *J Urol*. 2008; 179(4):1587–1592. [PubMed: 18295257]
- Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, Lagarde J, Veeravalli L, Ruan X, Ruan Y, Lassmann T, Carninci P, Brown JB, Lipovich L, Gonzalez JM, Thomas M, Davis CA, Shiekhata R, Gingeras TR, Hubbard TJ, Notredame C, Harrow J, Guigo R. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res*. 2012; 22(9):1775–1789. [PubMed: 22955988]
- Erho N, Crisan A, Vergara IA, Mitra AP, Ghadessi M, Buerki C, Bergstralh EJ, Kollmeyer T, Fink S, Haddad Z, Zimmermann B, Sierocinski T, Ballman KV, Triche TJ, Black PC, Karnes RJ, Klee G, Davicioni E, Jenkins RB. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS ONE*. 2013; 8(6):e66855. [PubMed: 23826159]
- Ferro M, Bruzzese D, Perdoni S, Marino A, Mazzarella C, Perruolo G, D'Esposito V, Cosimato V, Buonerba C, Di Lorenzo G, Musi G, De Cobelli O, Chun FK, Terracciano D. Prostate Health Index (Phi) and Prostate Cancer Antigen 3 (PCA3) significantly improve prostate cancer detection at initial biopsy in a total PSA range of 2-10 ng/ml. *PLoS ONE*. 2013; 8(7):e67687. [PubMed: 23861782]
- Fraser M, Berlin A, Bristow RG, van der Kwast T. Genomic, pathological, and clinical heterogeneity as drivers of personalized medicine in prostate cancer. *Urol Oncol*. 2015; 33(2):85–94. [PubMed: 24768356]
- Freedland SJ, Gerber L, Reid J, Welbourn W, Tikishvili E, Park J, Younus A, Gutin A, Sangale Z, Lanchbury JS, Salama JK, Stone S. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *Int J Radiat Oncol Biol Phys*. 2013; 86(5):848–853. [PubMed: 23755923]
- Gasi Tandefelt D, Boormans JL, van der Korput HA, Jenster GW, Trapman J. A 36-gene signature predicts clinical progression in a subgroup of ERG-positive prostate cancers. *Eur Urol*. 2013; 64(6):941–950. [PubMed: 23490727]
- Gittelman MC, Hertzman B, Bailen J, Williams T, Koziol I, Henderson RJ, Efros M, Bidair M, Ward JF. PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study. *J Urol*. 2013; 190(1):64–69. [PubMed: 23416644]
- Glinsky GV, Glinskii AB, Stephenson AJ, Hoffman RM, Gerald WL. Gene expression profiling predicts clinical outcome of prostate cancer. *J Clin Invest*. 2004; 113(6):913–923. [PubMed: 15067324]
- Groscopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, Brentano S, Mathis J, Pham J, Meyer T, Cass M, Hodge P, Macairan ML, Marks LS, Rittenhouse H. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. *Clin Chem*. 2006; 52(6):1089–1095. [PubMed: 16627561]
- Guo Z, Yang X, Sun F, Jiang R, Linn DE, Chen H, Chen H, Kong X, Melamed J, Tepper CG, Kung HJ, Brodie AM, Edwards J, Qiu Y. A novel androgen receptor splice variant is up-regulated during prostate cancer progression and promotes androgen depletion-resistant growth. *Cancer Res*. 2009; 69(6):2305–2313. [PubMed: 19244107]
- Haese A, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PF, Huland H, Abbou CC, Remzi M, Tinzl M, Feyerabend S, Stillebroer AB, van Gils MP, Schalken JA. Clinical utility of the PCA3 urine assay in European men scheduled for repeat biopsy. *Eur Urol*. 2008; 54(5):1081–1088. [PubMed: 18602209]

- Hansen J, Auprich M, Ahyai SA, de la Taille A, van Poppel H, Marberger M, Stenzl A, Mulders PF, Huland H, Fisch M, Abbou CC, Schalken JA, Fradet Y, Marks LS, Ellis W, Partin AW, Pummer K, Graefen M, Haese A, Walz J, Briganti A, Shariat SF, Chun FK. Initial prostate biopsy: development and internal validation of a biopsy-specific nomogram based on the prostate cancer antigen 3 assay. *Eur Urol*. 2013; 63(2):201–209. [PubMed: 22854248]
- Harrow J, Frankish A, Gonzalez JM, Tapanari E, Diekhans M, Kokocinski F, Aken BL, Barrell D, Zadissa A, Searle S, Barnes I, Bignell A, Boychenko V, Hunt T, Kay M, Mukherjee G, Rajan J, Despacio-Reyes G, Saunders G, Steward C, Harte R, Lin M, Howald C, Tanzer A, Derrien T, Chrast J, Walters N, Balasubramanian S, Pei B, Tress M, Rodriguez JM, Ezkurdia I, van Baren J, Brent M, Haussler D, Kellis M, Valencia A, Reymond A, Gerstein M, Guigo R, Hubbard TJ. GENCODE: the reference human genome annotation for The ENCODE Project. *Genome Res*. 2012; 22(9):1760–1774. [PubMed: 22955987]
- Hessels D, Klein Gunnewiek JM, van Oort I, Karthaus HF, van Leenders GJ, van Balken B, Kiemeney LA, Witjes JA, Schalken JA. DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. *Eur Urol*. 2003; 44(1):8–15. [PubMed: 12814669]
- Hoogland AM, Jenster G, van Weerden WM, Trapman J, van der Kwast T, Roobol MJ, Schroder FH, Wildhagen MF, van Leenders GJ. ERG immunohistochemistry is not predictive for PSA recurrence, local recurrence or overall survival after radical prostatectomy for prostate cancer. *Mod Pathol*. 2012; 25(3):471–479. [PubMed: 22080055]
- Hornberg E, Ylitalo EB, Crnalic S, Antti H, Stattin P, Widmark A, Bergh A, Wikstrom P. Expression of androgen receptor splice variants in prostate cancer bone metastases is associated with castration-resistance and short survival. *PLoS ONE*. 2011; 6(4):e19059. [PubMed: 21552559]
- Hu R, Dunn TA, Wei S, Isharwal S, Veltri RW, Humphreys E, Han M, Partin AW, Vessella RL, Isaacs WB, Bova GS, Luo J. Ligand-independent androgen receptor variants derived from splicing of cryptic exons signify hormone-refractory prostate cancer. *Cancer Res*. 2009; 69(1):16–22. [PubMed: 19117982]
- Hu R, Isaacs WB, Luo J. A snapshot of the expression signature of androgen receptor splicing variants and their distinctive transcriptional activities. *Prostate*. 2011; 71(15):1656–1667. [PubMed: 21446008]
- Hu R, Lu C, Mostaghel EA, Yegnasubramanian S, Gurel M, Tannahill C, Edwards J, Isaacs WB, Nelson PS, Bluemn E, Plymate SR, Luo J. Distinct transcriptional programs mediated by the ligand-dependent full-length androgen receptor and its splice variants in castration-resistant prostate cancer. *Cancer Res*. 2012; 72(14):3457–3462. [PubMed: 22710436]
- Irshad S, Bansal M, Castillo-Martin M, Zheng T, Aytes A, Wenske S, Le Magnen C, Guarnieri P, Sumazin P, Benson MC, Shen MM, Califano A, Abate-Shen C. A molecular signature predictive of indolent prostate cancer. *Sci Transl Med*. 2013; 5(202):202ra122.
- Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, Poliakov A, Cao X, Dhanasekaran SM, Wu YM, Robinson DR, Beer DG, Feng FY, Iyer HK, Chinnaiyan AM. The landscape of long noncoding RNAs in the human transcriptome. *Nat Genet*. 2015; 47:199–208. [PubMed: 25599403]
- Kalnina Z, Zayakin P, Silina K, Line A. Alterations of pre-mRNA splicing in cancer. *Genes Chromosomes Cancer*. 2005; 42(4):342–357. [PubMed: 15648050]
- Karnes RJ, Bergstralh EJ, Davicioni E, Ghadessi M, Buerki C, Mitra AP, Crisan A, Erho N, Vergara IA, Lam LL, Carlson R, Thompson DJ, Haddad Z, Zimmermann B, Sierocinski T, Triche TJ, Kollmeyer T, Ballman KV, Black PC, Klee GG, Jenkins RB. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. *J Urol*. 2013; 190(6):2047–2053. [PubMed: 23770138]
- Khani F, Mosquera JM, Park K, Blattner M, O'Reilly C, MacDonald TY, Chen Z, Srivastava A, Tewari AK, Barbieri CE, Rubin MA, Robinson BD. Evidence for molecular differences in prostate cancer between African American and Caucasian men. *Clin Cancer Res*. 2014; 20(18):4925–4934. [PubMed: 25056375]
- Khor LY, Bae K, Paulus R, Al-Saleem T, Hammond ME, Grignon DJ, Che M, Venkatesan V, Byhardt RW, Rotman M, Hanks GE, Sandler HM, Pollack A. MDM2 and Ki-67 predict for distant metastasis and mortality in men treated with radiotherapy and androgen deprivation for prostate cancer: RTOG 92-02. *J Clin Oncol*. 2009; 27(19):3177–3184. [PubMed: 19470936]

- Klein EA, Cooperberg MR, Magi-Galluzzi C, Simko JP, Falzarano SM, Maddala T, Chan JM, Li J, Cowan JE, Tsiatis AC, Cherbavaz DB, Pelham RJ, Tenggara-Hunter I, Baehner FL, Knezevic D, Febbo PG, Shak S, Kattan MW, Lee M, Carroll PR. A 17-gene Assay to Predict Prostate Cancer Aggressiveness in the Context of Gleason Grade Heterogeneity, Tumor Multifocality, and Biopsy Undersampling. *Eur Urol*. 2014; 66(3):550–560. [PubMed: 24836057]
- Klein EA, Yousefi K, Haddad Z, Choeurng V, Buerki C, Stephenson AJ, Li J, Kattan MW, Magi-Galluzzi C, Davicioni E. A Genomic Classifier Improves Prediction of Metastatic Disease Within 5 Years After Surgery in Node-negative High-risk Prostate Cancer Patients Managed by Radical Prostatectomy Without Adjuvant Therapy. *Eur Urol*. 2015; 67(1):778–786. [PubMed: 25466945]
- Knezevic D, Goddard AD, Natraj N, Cherbavaz DB, Clark-Langone KM, Snable J, Watson D, Falzarano SM, Magi-Galluzzi C, Klein EA, Quale C. Analytical validation of the Oncotype DX prostate cancer assay - a clinical RT-PCR assay optimized for prostate needle biopsies. *BMC Genomics*. 2013; 14:690. [PubMed: 24103217]
- Leyten GH, Hessels D, Jannink SA, Smit FP, de Jong H, Cornel EB, de Reijke TM, Vergunst H, Kil P, Knipscheer BC, van Oort IM, Mulders PF, Hulsbergen-van de Kaa CA, Schalken JA. Prospective multicentre evaluation of PCA3 and TMPRSS2-ERG gene fusions as diagnostic and prognostic urinary biomarkers for prostate cancer. *Eur Urol*. 2014; 65(3):534–542. [PubMed: 23201468]
- Li Y, Hwang TH, Oseth LA, Hauge A, Vessella RL, Schmechel SC, Hirsch B, Beckman KB, Silverstein KA, Dehm SM. AR intragenic deletions linked to androgen receptor splice variant expression and activity in models of prostate cancer progression. *Oncogene*. 2012; 31(45):4759–4767. [PubMed: 22266865]
- Lin DW, Newcomb LF, Brown EC, Brooks JD, Carroll PR, Feng Z, Gleave ME, Lance RS, Sanda MG, Thompson IM, Wei JT, Nelson PS, Canary Prostate Active Surveillance Study, I. Urinary TMPRSS2:ERG and PCA3 in an active surveillance cohort: results from a baseline analysis in the Canary Prostate Active Surveillance Study. *Clin Cancer Res*. 2013; 19(9):2442–2450. [PubMed: 23515404]
- Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications after prostate biopsy: data from SEER-Medicare. *J Urol*. 2011; 186(5):1830–1834. [PubMed: 21944136]
- Long Q, Xu J, Osunkoya AO, Sannigrahi S, Johnson BA, Zhou W, Gillespie T, Park JY, Nam RK, Sugar L, Stanimirovic A, Seth AK, Petros JA, Moreno CS. Global transcriptome analysis of formalin-fixed prostate cancer specimens identifies biomarkers of disease recurrence. *Cancer Res*. 2014; 74(12):3228–3237. [PubMed: 24713434]
- Magi-Galluzzi C, Tsusuki T, Elson P, Simmerman K, LaFargue C, Esgueva R, Klein E, Rubin MA, Zhou M. TMPRSS2-ERG gene fusion prevalence and class are significantly different in prostate cancer of Caucasian, African-American and Japanese patients. *Prostate*. 2011; 71(5):489–497. [PubMed: 20878952]
- Malhotra S, Lapointe J, Salari K, Higgins JP, Ferrari M, Montgomery K, van de Rijn M, Brooks JD, Pollack JR. A tri-marker proliferation index predicts biochemical recurrence after surgery for prostate cancer. *PLoS ONE*. 2011; 6(5):e20293. [PubMed: 21629784]
- Mashal RD, Lester S, Corless C, Richie JP, Chandra R, Propert KJ, Dutta A. Expression of cell cycle-regulated proteins in prostate cancer. *Cancer Res*. 1996; 56(18):4159–4163. [PubMed: 8797586]
- Mehra R, Shi Y, Udager AM, Prensner JR, Sahu A, Iyer MK, Siddiqui J, Cao X, Wei J, Jiang H, Feng FY, Chinnaiyan AM. A novel RNA in situ hybridization assay for the long noncoding RNA SchLAP1 predicts poor clinical outcome after radical prostatectomy in clinically localized prostate cancer. *Neoplasia*. 2014; 16(12):1121–1127. [PubMed: 25499224]
- Miller AB. New data on prostate-cancer mortality after PSA screening. *N Engl J Med*. 2012; 366(11):1047–1048. [PubMed: 22417259]
- Minner S, Enodien M, Sirma H, Luebke AM, Krohn A, Mayer PS, Simon R, Tennstedt P, Muller J, Scholz L, Brase JC, Liu AY, Schluter H, Pantel K, Schumacher U, Bokemeyer C, Steuber T, Graefen M, Sauter G, Schlomm T. ERG status is unrelated to PSA recurrence in radically operated prostate cancer in the absence of antihormonal therapy. *Clin Cancer Res*. 2011; 17(18):5878–5888. [PubMed: 21791629]
- Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Brian KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen BS, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M. Circulating microRNAs as stable

- blood-based markers for cancer detection. *Proc Natl Acad Sci U S A*. 2008; 105(30):10513–10518. [PubMed: 18663219]
- Miyagi Y, Sasaki T, Fujinami K, Sano J, Senga Y, Miura T, Kameda Y, Sakuma Y, Nakamura Y, Harada M, Tsuchiya E. ETS family-associated gene fusions in Japanese prostate cancer: analysis of 194 radical prostatectomy samples. *Mod Pathol*. 2010; 23(11):1492–1498. [PubMed: 20693979]
- Mosquera JM, Mehra R, Regan MM, Perner S, Genega EM, Bueti G, Shah RB, Gaston S, Tomlins SA, Wei JT, Kearney MC, Johnson LA, Tang JM, Chinnaiyan AM, Rubin MA, Sanda MG. Prevalence of TMPRSS2-ERG fusion prostate cancer among men undergoing prostate biopsy in the United States. *Clin Cancer Res*. 2009; 15(14):4706–4711. [PubMed: 19584163]
- Mosquera JM, Perner S, Genega EM, Sanda M, Hofer MD, Mertz KD, Paris PL, Simko J, Bismar TA, Ayala G, Shah RB, Loda M, Rubin MA. Characterization of TMPRSS2-ERG fusion high-grade prostatic intraepithelial neoplasia and potential clinical implications. *Clin Cancer Res*. 2008; 14(11):3380–3385. [PubMed: 18519767]
- Moyer VA, U.S. Preventive Services Task Force. Screening for prostate cancer: U. S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012; 157(2):120–134. [PubMed: 22801674]
- Nam RK, Sugar L, Yang W, Srivastava S, Klotz LH, Yang LY, Stanimirovic A, Encioiu E, Neill M, Loblaw DA, Trachtenberg J, Narod SA, Seth A. Expression of the TMPRSS2:ERG fusion gene predicts cancer recurrence after surgery for localised prostate cancer. *Br J Cancer*. 2007; 97(12):1690–1695. [PubMed: 17971772]
- Nguyen HC, Xie W, Yang M, Hsieh CL, Drouin S, Lee GS, Kantoff PW. Expression differences of circulating microRNAs in metastatic castration resistant prostate cancer and low-risk, localized prostate cancer. *Prostate*. 2013; 73(4):346–354. [PubMed: 22887127]
- Olmos D, Brewer D, Clark J, Danila DC, Parker C, Attard G, Fleisher M, Reid AH, Castro E, Sandhu SK, Barwell L, Oommen NB, Carreira S, Drake CG, Jones R, Cooper CS, Scher HI, de Bono JS. Prognostic value of blood mRNA expression signatures in castration-resistant prostate cancer: a prospective, two-stage study. *Lancet Oncol*. 2012; 13(11):1114–1124. [PubMed: 23059046]
- Park K, Dalton JT, Narayanan R, Barbieri CE, Hancock ML, Bostwick DG, Steiner MS, Rubin MA. TMPRSS2:ERG gene fusion predicts subsequent detection of prostate cancer in patients with high-grade prostatic intraepithelial neoplasia. *J Clin Oncol*. 2014; 32(3):206–211. [PubMed: 24297949]
- Peng Z, Skoog L, Hellborg H, Jonstam G, Wingmo IL, Hjalmar-Eriksson M, Harmenberg U, Cedermark GC, Andersson K, Ahrlund-Richter L, Pramana S, Pawitan Y, Nister M, Nilsson S, Li C. An expression signature at diagnosis to estimate prostate cancer patients' overall survival. *Prostate Cancer Prostatic Dis*. 2014; 17(1):81–90. [PubMed: 24394557]
- Penney KL, Sinnott JA, Fall K, Pawitan Y, Hoshida Y, Kraft P, Stark JR, Fiorentino M, Perner S, Finn S, Calza S, Flavin R, Freedman ML, Setlur S, Sesso HD, Andersson SO, Martin N, Kantoff PW, Johansson JE, Adami HO, Rubin MA, Loda M, Golub TR, Andren O, Stampfer MJ, Mucci LA. mRNA expression signature of Gleason grade predicts lethal prostate cancer. *J Clin Oncol*. 2011; 29(17):2391–2396. [PubMed: 21537050]
- Perdona S, Bruzzese D, Ferro M, Autorino R, Marino A, Mazzeo C, Perruolo G, Longo M, Spinelli R, Di Lorenzo G, Oliva A, De Sio M, Damiano R, Altieri V, Terracciano D. Prostate health index (phi) and prostate cancer antigen 3 (PCA3) significantly improve diagnostic accuracy in patients undergoing prostate biopsy. *Prostate*. 2013; 73(3):227–235. [PubMed: 22821756]
- Perner S, Demichelis F, Beroukhim R, Schmidt FH, Mosquera JM, Setlur S, Tchinda J, Tomlins SA, Hofer MD, Pienta KG, Kuefer R, Vessella R, Sun XW, Meyerson M, Lee C, Sellers WR, Chinnaiyan AM, Rubin MA. TMPRSS2:ERG fusion-associated deletions provide insight into the heterogeneity of prostate cancer. *Cancer Res*. 2006; 66(17):8337–8341. [PubMed: 16951139]
- Perner S, Mosquera JM, Demichelis F, Hofer MD, Paris PL, Simko J, Collins C, Bismar TA, Chinnaiyan AM, De Marzo AM, Rubin MA. TMPRSS2-ERG fusion prostate cancer: an early molecular event associated with invasion. *Am J Surg Pathol*. 2007; 31(6):882–888. [PubMed: 17527075]
- Petrovics G, Zhang W, Makarem M, Street JP, Connelly R, Sun L, Sesterhenn IA, Srikantan V, Moul JW, Srivastava S. Elevated expression of PCGEM1, a prostate-specific gene with cell growth-

promoting function, is associated with high-risk prostate cancer patients. *Oncogene*. 2004; 23(2): 605–611. [PubMed: 14724589]

- Pettersson A, Graff RE, Bauer SR, Pitt MJ, Lis RT, Stack EC, Martin NE, Kunz L, Penney KL, Ligon AH, Suppan C, Flavin R, Sesso HD, Rider JR, Sweeney C, Stampfer MJ, Fiorentino M, Kantoff PW, Sanda MG, Giovannucci EL, Ding EL, Loda M, Mucci LA. The TMPRSS2:ERG Rearrangement, ERG Expression, and Prostate Cancer Outcomes: A Cohort Study and Meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2012; 21(9):1497–1509. [PubMed: 22736790]
- Potosky AL, Legler J, Albertsen PC, Stanford JL, Gilliland FD, Hamilton AS, Eley JW, Stephenson RA, Harlan LC. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. *J Natl Cancer Inst*. 2000; 92(19):1582–1592. [PubMed: 11018094]
- Prensner JR, Iyer MK, Balbin OA, Dhanasekaran SM, Cao Q, Brenner JC, Laxman B, Asangani IA, Grasso CS, Kominsky HD, Cao X, Jing X, Wang X, Siddiqui J, Wei JT, Robinson D, Iyer HK, Palanisamy N, Maher CA, Chinnaiyan AM. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. *Nat Biotechnol*. 2011; 29(8):742–749. [PubMed: 21804560]
- Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, Vergara IA, Davicioni E, Erho N, Ghadessi M, Jenkins RB, Triche TJ, Malik R, Bedenis R, McGregor N, Ma T, Chen W, Han S, Jing X, Cao X, Wang X, Chandler B, Yan W, Siddiqui J, Kunju LP, Dhanasekaran SM, Pienta KJ, Feng FY, Chinnaiyan AM. The long noncoding RNA SchLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat Genet*. 2013; 45(11):1392–1398. [PubMed: 24076601]
- Prensner JR, Sahu A, Iyer MK, Malik R, Chandler B, Asangani IA, Poliakov A, Vergara IA, Alshalalfa M, Jenkins RB, Davicioni E, Feng FY, Chinnaiyan AM. The lncRNAs PCGEM1 and PRNCR1 are not implicated in castration resistant prostate cancer. *Oncotarget*. 2014a; 5(6):1434–1438. [PubMed: 24727738]
- Prensner JR, Zhao S, Erho N, Schipper M, Iyer MK, Dhanasekaran SM, Magi-Galluzzi C, Mehra R, Sahu A, Siddiqui J, Davicioni E, Den RB, Dicker AP, Karnes RJ, Wei JT, Klein EA, Jenkins RB, Chinnaiyan AM, Feng FY. RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SchLAP1. *Lancet Oncol*. 2014b; 15(13):1469–1480. [PubMed: 25456366]
- Qu Y, Dai B, Ye D, Kong Y, Chang K, Jia Z, Yang X, Zhang H, Zhu Y, Shi G. Constitutively Active AR-V7 Plays an Essential Role in the Development and Progression of Castration-Resistant Prostate Cancer. *Sci Rep*. 2015; 5:7654. [PubMed: 25563505]
- Ramos CG, Valdevenito R, Vergara I, Anabalón P, Sánchez C, Fulla J. PCA3 sensitivity and specificity for prostate cancer detection in patients with abnormal PSA and/or suspicious digital rectal examination. First Latin American experience. *Urol Oncol*. 2013; 31(8):1522–1526. [PubMed: 22687565]
- Ren S, Liu Y, Xu W, Sun Y, Lu J, Wang F, Wei M, Shen J, Hou J, Gao X, Xu C, Huang J, Zhao Y, Sun Y. Long noncoding RNA MALAT-1 is a new potential therapeutic target for castration resistant prostate cancer. *J Urol*. 2013a; 190(6):2278–2287. [PubMed: 23845456]
- Ren S, Wang F, Shen J, Sun Y, Xu W, Lu J, Wei M, Xu C, Wu C, Zhang Z, Gao X, Liu Z, Hou J, Huang J, Sun Y. Long non-coding RNA metastasis associated in lung adenocarcinoma transcript 1 derived miniRNA as a novel plasma-based biomarker for diagnosing prostate cancer. *Eur J Cancer*. 2013b; 49(13):2949–2959. [PubMed: 23726266]
- Rosen P, Pfister D, Young D, Petrovics G, Chen Y, Cullen J, Böhm D, Perner S, Dobi A, McLeod DG, Sesterhenn IA, Srivastava S. Differences in frequency of ERG oncoprotein expression between index tumors of Caucasian and African American patients with prostate cancer. *Urology*. 2012; 80(4):749–753. [PubMed: 22950997]
- Ross AE, Feng FY, Ghadessi M, Erho N, Crisan A, Buerki C, Sundi D, Mitra AP, Vergara IA, Thompson DJ, Triche TJ, Davicioni E, Bergstralh EJ, Jenkins RB, Karnes RJ, Schaeffer EM. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. *Prostate Cancer Prostatic Dis*. 2014; 17(1):64–69. [PubMed: 24145624]
- Ross RW, Galsky MD, Scher HI, Magidson J, Wassmann K, Lee GS, Katz L, Subudhi SK, Anand A, Fleisher M, Kantoff PW, Oh WK. A whole-blood RNA transcript-based prognostic model in men

- with castration-resistant prostate cancer: a prospective study. *Lancet Oncol.* 2012; 13(11):1105–1113. [PubMed: 23059047]
- Rowley JD. Chromosome translocations: dangerous liaisons revisited. *Nat Rev Cancer.* 2001; 1(3): 245–250. [PubMed: 11902580]
- Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, Lin X, Greenfield TK, Litwin MS, Saigal CS, Mahadevan A, Klein E, Kibel A, Pisters LL, Kuban D, Kaplan I, Wood D, Ciezki J, Shah N, Wei JT. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med.* 2008; 358(12):1250–1261. [PubMed: 18354103]
- Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Paez A, Maattanen L, Bangma CH, Aus G, Carlsson S, Villers A, Rebillard X, van der Kwast T, Kujala PM, Blijenberg BG, Stenman UH, Huber A, Taari K, Hakama M, Moss SM, de Koning HJ, Auvinen A. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med.* 2012; 366(11):981–990. [PubMed: 22417251]
- Selth LA, Townley S, Gillis JL, Ochnik AM, Murti K, Macfarlane RJ, Chi KN, Marshall VR, Tilley WD, Butler LM. Discovery of circulating microRNAs associated with human prostate cancer using a mouse model of disease. *Int J Cancer.* 2012; 131(3):652–661. [PubMed: 22052531]
- Singh D, Febbo PG, Ross K, Jackson DG, Manola J, Ladd C, Tamayo P, Renshaw AA, D'Amico AV, Richie JP, Lander ES, Loda M, Kantoff PW, Golub TR, Sellers WR. Gene expression correlates of clinical prostate cancer behavior. *Cancer Cell.* 2002; 1(2):203–209. [PubMed: 12086878]
- Smith RA, Manassaram-Baptiste D, Brooks D, Doroshenko M, Fedewa S, Saslow D, Brawley OW, Wender R. Cancer screening in the United States, 2015: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* 2015; 65(1):30–54. [PubMed: 25581023]
- Sowalsky AG, Xia Z, Wang L, Zhao H, Chen S, Buble GJ, Balk SP, Li W. Whole transcriptome sequencing reveals extensive unspliced mRNA in metastatic castration-resistant prostate cancer. *Mol Cancer Res.* 2015; 13(1):98–106. [PubMed: 25189356]
- Srikantan V, Zou Z, Petrovics G, Xu L, Augustus M, Davis L, Livezey JR, Connell T, Sesterhenn IA, Yoshino K, Buzard GS, Mostofi FK, McLeod DG, Moul JW, Srivastava S. PCGEM1, a prostate-specific gene, is overexpressed in prostate cancer. *Proc Natl Acad Sci U S A.* 2000; 97(22): 12216–12221. [PubMed: 11050243]
- Stephan C, Jung K, Semjonow A, Schulze-Forster K, Cammann H, Hu X, Meyer HA, Bogemann M, Miller K, Friedersdorff F. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]prostate-specific antigen-based prostate health index for detection of prostate cancer. *Clin Chem.* 2013; 59(1):280–288. [PubMed: 23213079]
- Sun S, Sprenger CC, Vessella RL, Haugk K, Soriano K, Mostaghel EA, Page ST, Coleman IM, Nguyen HM, Sun H, Nelson PS, Plymate SR. Castration resistance in human prostate cancer is conferred by a frequently occurring androgen receptor splice variant. *J Clin Invest.* 2010; 120(8): 2715–2730. [PubMed: 20644256]
- The ENCODE Project Consortium. Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. *Nature.* 2007; 447(7146):799–816. [PubMed: 17571346]
- Tinzl M, Marberger M, Horvath S, Chypre C. DD3PCA3 RNA analysis in urine--a new perspective for detecting prostate cancer. *Eur Urol.* 2004; 46(2):182–186. [PubMed: 15245811]
- Tombal B, Andriole GL, de la Taille A, Gontero P, Haese A, Remzi M, Speakman M, Smets L, Stoevelaar H. Clinical judgment versus biomarker prostate cancer gene 3: which is best when determining the need for repeat prostate biopsy? *Urology.* 2013; 81(5):998–1004. [PubMed: 23523291]
- Tomlins SA, Aubin SM, Siddiqui J, Lonigro RJ, Sefton-Miller L, Miick S, Williamsen S, Hodge P, Meinke J, Blase A, Penabell Y, Day JR, Varambally R, Han B, Wood D, Wang L, Sanda MG, Rubin MA, Rhodes DR, Hollenbeck B, Sakamoto K, Silberstein JL, Fradet Y, Amberson JB, Meyers S, Palanisamy N, Rittenhouse H, Wei JT, Grosskopf J, Chinnaiyan AM. Urine TMPRSS2:ERG fusion transcript stratifies prostate cancer risk in men with elevated serum PSA. *Sci Transl Med.* 2011; 3(94):94ra72.

- Tomlins SA, Mehra R, Rhodes DR, Smith LR, Roulston D, Helgeson BE, Cao X, Wei JT, Rubin MA, Shah RB, Chinnaiyan AM. TMPRSS2:ETV4 gene fusions define a third molecular subtype of prostate cancer. *Cancer Res.* 2006; 66(7):3396–3400. [PubMed: 16585160]
- Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, Varambally S, Cao X, Tchinda J, Kuefer R, Lee C, Montie JE, Shah RB, Pienta KJ, Rubin MA, Chinnaiyan AM. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science.* 2005; 310(5748):644–648. [PubMed: 16254181]
- van Gils MP, Hessels D, van Hooij O, Jannink SA, Peelen WP, Hanssen SL, Witjes JA, Cornel EB, Karthaus HF, Smits GA, Dijkman GA, Mulders PF, Schalken JA. The time-resolved fluorescence-based PCA3 test on urinary sediments after digital rectal examination; a Dutch multicenter validation of the diagnostic performance. *Clin Cancer Res.* 2007; 13(3):939–943. [PubMed: 17289888]
- Varambally S, Yu J, Laxman B, Rhodes DR, Mehra R, Tomlins SA, Shah RB, Chandran U, Monzon FA, Becich MJ, Wei JT, Pienta KJ, Ghosh D, Rubin MA, Chinnaiyan AM. Integrative genomic and proteomic analysis of prostate cancer reveals signatures of metastatic progression. *Cancer Cell.* 2005; 8(5):393–406. [PubMed: 16286247]
- Venables JP, Klinck R, Koh C, Gervais-Bird J, Bramard A, Inkel L, Durand M, Couture S, Froehlich U, Lapointe E, Lucier JF, Thibault P, Rancourt C, Tremblay K, Prinos P, Chabot B, Elela SA. Cancer-associated regulation of alternative splicing. *Nat Struct Mol Biol.* 2009; 16(6):670–676. [PubMed: 19448617]
- Vlaeminck-Guillem V, Bandel M, Cottancin M, Rodriguez-Lafrasse C, Bohbot JM, Sednaoui P. Chronic prostatitis does not influence urinary PCA3 score. *Prostate.* 2012; 72(5):549–554. [PubMed: 21761426]
- Wach S, Nolte E, Szczyrba J, Stohr R, Hartmann A, Orntoft T, Dyrskjot L, Eltze E, Wieland W, Keck B, Ekici AB, Grasser F, Wullich B. MicroRNA profiles of prostate carcinoma detected by multiplatform microRNA screening. *Int J Cancer.* 2012; 130(3):611–621. [PubMed: 21400514]
- Wang F, Ren S, Chen R, Lu J, Shi X, Zhu Y, Zhang W, Jing T, Zhang C, Shen J, Xu C, Wang H, Wang H, Wang Y, Liu B, Li Y, Fang Z, Guo F, Qiao M, Wu C, Wei Q, Xu D, Shen D, Lu X, Gao X, Hou J, Sun Y. Development and prospective multicenter evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer. *Oncotarget.* 2014; 5(22):11091–11102. [PubMed: 25526029]
- Watson PA, Chen YF, Balbas MD, Wongvipat J, Socci ND, Viale A, Kim K, Sawyers CL. Constitutively active androgen receptor splice variants expressed in castration-resistant prostate cancer require full-length androgen receptor. *Proc Natl Acad Sci U S A.* 2010; 107(39):16759–16765. [PubMed: 20823238]
- Wei JT, Feng Z, Partin AW, Brown E, Thompson I, Sokoll L, Chan DW, Lotan Y, Kibel AS, Busby JE, Bidair M, Lin DW, Taneja SS, Viterbo R, Joon AY, Dahlgren J, Kagan J, Srivastava S, Sanda MG. Can Urinary PCA3 Supplement PSA in the Early Detection of Prostate Cancer? *J Clin Oncol.* 2014; 32(36):4066–4072. [PubMed: 25385735]
- Welch HG, Fisher ES, Gottlieb DJ, Barry MJ. Detection of prostate cancer via biopsy in the Medicare-SEER population during the PSA era. *J Natl Cancer Inst.* 2007; 99(18):1395–1400. [PubMed: 17848671]
- Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Gilhooly P, Grob BM, Nsouli I, Iyer P, Cartagena R, Snider G, Roehrborn C, Sharifi R, Blank W, Pandya P, Andriole GL, Culkin D, Wheeler T. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med.* 2012; 367(3):203–213. [PubMed: 22808955]
- Young A, Palanisamy N, Siddiqui J, Wood DP, Wei JT, Chinnaiyan AM, Kunju LP, Tomlins SA. Correlation of urine TMPRSS2:ERG and PCA3 to ERG+ and total prostate cancer burden. *Am J Clin Pathol.* 2012; 138(5):685–696. [PubMed: 23086769]
- Yu YP, Landsittel D, Jing L, Nelson J, Ren B, Liu L, McDonald C, Thomas R, Dhir R, Finkelstein S, Michalopoulos G, Becich M, Luo JH. Gene expression alterations in prostate cancer predicting tumor aggression and preceding development of malignancy. *J Clin Oncol.* 2004; 22(14):2790–2799. [PubMed: 15254046]

Zhang X, Morrissey C, Sun S, Ketchandji M, Nelson PS, True LD, Vakar-Lopez F, Vessella RL, Plymate SR. Androgen receptor variants occur frequently in castration resistant prostate cancer metastases. PLoS ONE. 2011; 6(11):e27970. [PubMed: 22114732]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Non-coding RNAs under investigation as prostate cancer biomarkers.

ncRNA	Tissues	Findings	Cohorts	References
miR-141	Prostate Serum	<ul style="list-style-type: none"> Increased in PCa and Mets Associated with Gleason score Highly expressed in serum from mCRPC patients Did not stratify patients for risk of BCR 	BCCA, DFCI, MSKCC, UMCHE, UM, UW	(Brase et al., 2011; Cheng et al., 2013; Mitchell et al., 2008; Nguyen et al., 2013; Selth et al., 2012)
miR-375	Prostate Serum	<ul style="list-style-type: none"> Not expressed in surrounding stroma Increased in PCa and Mets Highly expressed in serum from mCRPC patients 	BCCA, DFCI, MSKCC, UMCHE, UM, UMu, UR, UW	(Brase et al., 2011; Cheng et al., 2013; Nguyen et al., 2013; Selth et al., 2012; Wach et al., 2012)
MALAT-1	Prostate Mets Serum Urine	<ul style="list-style-type: none"> Increased in PCa and Mets Associated with Gleason score and T stage Higher in serum and urine of patients later diagnosed with PCa from biopsy 	CH, CZH, WCH	(Ren et al., 2013a; Ren et al., 2013b; Wang et al., 2014)
NEAT1	Prostate	<ul style="list-style-type: none"> Increased in PCa and CRPC High NEAT1 expression associated with greater risk of BCR, and Mets 	MC, WCMC	(Chakravarty et al., 2014)
PCGEM1	Prostate	<ul style="list-style-type: none"> Increased in PCa AA and patients with family history more likely to have high PCGEM1 in PCa tissue Did not stratify patients for risk of PCSM 	BCM, CH, MC, UM, USUHS, WCMC, WRAMC	(Petrovics et al., 2004; Prensner et al., 2014a; Srikantan et al., 2000)
SChLAP1	Prostate Mets Urine	<ul style="list-style-type: none"> No expression in benign prostate Increased expression in PCa and Mets High SChLAP1 associated with greater risk of BCR, Mets, and PCSM Detected in urine, higher in patients grouped as intermediate/high risk from biopsy 	CC, EMC, MC, UM	(Mehra et al., 2014; Prensner et al., 2011; Prensner et al., 2013; Prensner et al., 2014b)

AA, African Americans; BCCA, British Columbia Cancer Agency; BCM, Baylor College of Medicine; BCR, Biochemical recurrence; CC, Cleveland Clinic; CH, Changhai Hospital; CRPC, Castration-resistant prostate cancer; CZH, Changzheng Hospital; DFCI, Dana-Farber Cancer Institute; EMC, Erasmus Medical Center; MC, Mayo Clinic; mCRPC, Metastatic castration-resistant prostate cancer; Mets, Metastases; MSKCC, Memorial Sloan-Kettering Cancer Center; PCa, Localized prostate cancer; PCSM, Prostate cancer-specific mortality; UM, University of Michigan; UMu, University of Munster; UMCHE, University Medical Center Hamburg-Eppendorf; UR, University of Regensburg; USUHS, Uniformed Services University of the Health Sciences; UW, University of Washington; WCH, West China Hospital; WCMC, Weill Cornell Medical College; WRAMC, Walter Reed Army Medical Center

Table 2

Commercially available multi-gene mRNA expression panels for prostate cancer.

Panel Name	Number of Genes	Signature Discovery Approach	Reference
Prolaris® – Myriad Genetics	31 CCP test genes 15 normalizers	<ul style="list-style-type: none"> ▪ Candidate gene approach ▪ 126 cell cycle and cellular proliferation genes tested in prostatectomy tissues 	Cuzick et al. (2011)
Oncotype DX® Prostate Cancer Assay – Genomic Health	12 GPS test genes 5 normalizers	<ul style="list-style-type: none"> ▪ Candidate gene approach ▪ 727 genes tested in prostatectomy tissues ▪ Refined panel of 81 genes tested in biopsies 	Klein et al. (2014)
Decipher® Prostate Cancer Classifier – GenomeDx	22 GC test genes Whole microarray normalization	<ul style="list-style-type: none"> ▪ Whole transcriptome analysis ▪ Affymetrix GeneChip® Human Exon 1.0 ST Array used to assess prostatectomy tissues 	Erho et al. (2013)

CCP, Cell Cycle Progression; GC, Genomic Classifier; GPS, Genomic Prostate Score

Table 3

Multi-gene mRNA expression panels with prognostic potential for prostate cancer.

PROGNOSTIC FOR BIOCHEMICAL RECURRENCE				
Reference	Tissue	Cohorts	Signature Discovery Approach	Number of Genes
Glinsky et al. (2004)	Prostate	Training: DFCI Validation: MSKCC	<ul style="list-style-type: none"> Over 12,000 genes measured in training set Three different gene expression signatures associated with BCR identified The combined panel (14 genes) and the three individual panels all had prognostic value 	14
Yu et al. (2004)	Prostate	Training: UP Validation: UM	<ul style="list-style-type: none"> Comprehensive gene expression analysis of training set performed by microarray 	70
Varambally et al. (2005)	Prostate	Training: UM, UP Validation: MSKCC	<ul style="list-style-type: none"> Proteomic analysis followed up with gene expression studies to find common genes 44 gene signature developed and then refined 	9
Bismar et al. (2006)	Prostate	Training: UM Validation: MSKCC	<ul style="list-style-type: none"> Proteomic analysis followed up with gene expression studies to find common genes 	12
Malhotra et al. (2011)	Prostate	Training: JH, KI, SU Validation: SU	<ul style="list-style-type: none"> Analysis of microarray data in training set showed genes involved in the cell cycle 	3
Gasi Tandefelt et al. (2013)	Prostate	Training: EMC Validation: MSKCC	<ul style="list-style-type: none"> Microarray analysis of training set Identified prognostic signature associated with BCR in ERG positive patients 	36
Irshad et al. (2013)	Prostate	Training: MSKCC, SWW, UP Validation: HICCC, MSKCC, SWW	<ul style="list-style-type: none"> 377 genes associated with senescence and aging measured in training set 19 gene panel developed and then refined Best performance amongst the low Gleason score group of patients 	3
Long et al. (2014)	Prostate	Training: AVAMC, MCC, UT Validation: MSKCC	<ul style="list-style-type: none"> Training set interrogated by whole transcriptome RNA sequencing 	24
PROGNOSTIC FOR MORTALITY				
Reference	Tissue	Cohorts	Signature Discovery Approach	Number of Genes
Penney et al. (2011)	Prostate	Training: SWW Validation: PHS	<ul style="list-style-type: none"> 6,100 genes measured to determine expression profiles of Gleason 6 and 8 tumors 	157
Olmos et al. (2012)	Blood	Training: RMH, BWSKC Validation: MSKCC	<ul style="list-style-type: none"> Gene expression in blood of CRPC patients measured by microarray 	9

PROGNOSTIC FOR BIOCHEMICAL RECURRENCE				
Reference	Tissue	Cohorts	Signature Discovery Approach	Number of Genes
Ross et al. (2012)	Blood	Training: DFCI Validation: MSKCC	■ Gene expression in blood of CRPC patients measured by microarray	6
Peng et al. (2014)	Prostate	Training: JH, KI, SU Validation: KI	■ 641 embryonic stem cell gene predictors tested in published arrays used as training set ■ 34 gene signature developed then refined	3

AVAMC, Atlanta Veteran's Administration Medical Center; BCR, Biochemical recurrence; BWSCC, Beatson West of Scotland Cancer Center; DFCI, Dana-Farber Cancer Institute; EMC, Erasmus Medical Center; HICCC, Herbert Irving Comprehensive Cancer Center; JH, Johns Hopkins University; KI, Karolinska Institute; MCC, Moffitt Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center; PHS, Physician's Health Study; RMH, Royal Marsden Hospital; SU, Stanford University; SWW, Swedish Watchful Waiting cohort; UM, University of Michigan; UP, University of Pittsburgh; UT, University of Toronto